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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 6/6/94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), (0) days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-17, 25-35 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 18-24 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1-17, 25-35 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

This application should be reviewed for errors.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 18-24 have been cancelled; claims 1-17 and 25-35 are examined in this Office Action.

The declaration submitted by Dr. Hammang is acknowledged, has been considered and is addressed, below.

The provisional rejection of claims 1-17 and 25-35 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-34 of copending application serial no. 08/010,829 in view of Cepko is maintained. Applicants' arguments, filed June 6, 1994, have been considered but not found to be persuasive. Applicants have stated that the rejection will not be addressed until there is an indication of allowable subject matter. Therefore, the rejection is maintained.

The rejection of claims 1-17 under 35 U.S.C. 101 because the claimed invention lacks patentable utility is maintained. Applicants have argued that the enclosed declaration by Dr. Hammang overcomes the rejection since the declaration shows that neurons can be remyelinated as claimed. However, contrary to such arguments, the claims as currently amended now required that the isolated neural stem cells be capable of differentiating into neurons, astrocytes and oligodendrocytes and the declaration states that the transplanted cells differentiated into oligodendrocytes. Therefore, it is not evident from the declaration that the the cells used by Dr. Hammang are capable of differentiating into neurons, astrocytes as well as oligodendrocytes. Therefore, the declaration is not commensurate with the newly amended claims and fails to overcome the rejection.

The rejection of claims 1-17 and 35 under 35 U.S.C. 112, first paragraph, is maintained. Regarding claim 1, Applicants have argued that claim 1 has been amended to address the term "associating" to read "causing the harvested precursor cells to come into contact with a demyelinated axon". However, the claim is neither clearly in vitro or in vivo and the usefulness of remyelinated axons in vitro is not apparent. Claim 7 remains rejected for the same reasons as claim 1.

The rejection of claims 1-17 under 35 U.S.C. 112, second paragraph, regarding the word "associating" is withdrawn in view of the amendments to the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to provide an adequate written description and for failing to adequately teach how to make and/or use the invention, i.e., failing to provide an enabling disclosure. The specification fails to disclose isolation of neural stem cells from the tissue of a donor. The specification does disclose use of a neural cell population derived from the brain and striata of embryonic day 15 rats but fails to disclose isolation of a stem cell population per se. Applicants have failed to provide evidence that neural stem cells were isolated from the neural cell population and the specification as originally filed fails to provide guidance to one of ordinary skill to enable one to obtain a neural stem cell population. It is well known in the art that there are a small number of definitive markers and lack of markers for specific situations such as stem cell detection (Saneto, page 30, top line). It would constitute undue experimentation by one of ordinary skill to develop

a marker to identify stem cells per se in order to obtain a method of isolating neural stem cells from tissues of a donor. The specification fails to provide evidence of any marker identifying stem cells or any procedure by which they may be separated from other cells types. Therefore, the specification is not enabling for claimed invention.

Claims 1-17 and 25-35 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the objection to the specification.

The rejection of claims 25-28 and 30 under 35 U.S.C. 102(b) as being anticipated by Hunter is maintained. Applicants have argued that Hunter is an inappropriate reference since Hunter starts with glial progenitor cells. However, Applicants' arguments are erroneous since Hunter does not start with progenitor cells but with the brain cells of neonatal (day 1-2) rats and the brain cells are known to contain the neural stem cells and secondly the cell cultures of Hunter contained the neural stem cells since Hunter did not remove them. See page 236, column 2, "Preparation of primary cultures" for the preparation of cell cultures containing stem cells. In addition, note that production of progeny cells is an inherent property of stem cells as has well been pointed out by Applicants. Therefore since Hunter inherently disclosed use of a cell population comprised of neural stem cells, Hunter therefore inherently discloses stem cells capable of differentiating into neurons, astrocytes and oligodendrocytes.

The rejection of claims 31-34 under 35 U.S.C. 102(b) as being anticipated by Hunter is withdrawn in view of the amendments to the claims. However, the amendments to the claims have necessitated new grounds of rejection, set forth below. Applicants' arguments are therefore moot.

The rejection of claim 29 under 35 U.S.C. 103 as being unpatentable over Hunter as applied to claims 25-28 and 30 above and further in of Morrison is maintained. Applicants have argued that the Morrison does not

disclose the proliferation of neural stem cells. However, Morrison was cited to disclose that that EGF stimulates the proliferation and differentiation of glial cells, not the proliferation of neural stem cells. Hunter was cited to disclose the proliferation of neural stem cells.

The rejection of claims 1, 3-6 and 35 under 35 U.S.C. 103 as being unpatentable over Boyles taken with Hunter, Gage and Masters is maintained. Applicants have argued that none of the references cited by the Examiner describe or suggest the proliferation of multipotent neural stem cells in culture to produce precursor cells which are used for remyelination. However, such arguments are not persuasive since both Hunter and Masters use cells derived from neonatal (Hunter) and day 1 rat brains (Masters) and both starting cell populations would be expected to contain the "neural stem cell".

Applicants have argued that the references do not teach the elements of isolation of multipotent neural stem cells and the proliferation of the cells in culture. However, contrary to such arguments, Hunter discloses preparation of glial cell progenitors and their culture on page 236, second column, last paragraph, and Masters discloses preparation of cells from 1 day old rat brains and the culture of the cells on page 119. Note that since Hunter and Masters started with brain tissue that the cell cultures obtained therefrom would necessarily contain the "neural stem cell" since neither Hunter nor Masters removed the "neural stem cells" from the cell cultures.

Applicants have argued that there is no motivation to combine the references. However, contrary to such arguments, it would have been obvious to one of ordinary skill to add the isolated precursor cells, cultured to produce oligodendrocytes and astrocytes, to the crushed nerves (demyelinated) of Boyles in order to effect remyelination. Boyles teaches that astrocytes and oligodendrocytes produce the lipid apoD necessary for the remyelination process. Therefore, it would have been obvious to one of ordinary skill to transplant the precursor cells, capable of differentiating into

astrocytes and oligodendrocytes, to the area of injury in order to produce apoD and thereby facilitate the injury repair process. Boyles provides the motivation to combine the references on page 17812, column 2, last paragraph, wherein it is stated "The function of apoD in neural tissue is unknown. However, the massive accumulation of apoD during nerve regeneration, coupled with its apparent production by the glial or supporting cells of the normal central and peripheral nervous systems, suggests that apoD, like apoE, plays a key role in both normal and regenerating neural tissue". Thus, contrary to arguments, the motivation to combine the references is found within the references.

Applicants have argued that claim 5 and 6 do not call for transplantation of a recipient's demyelinated axon but rather the isolation of a person's neural stem cells the proliferation of those stem cells to produce precursor cells and transplantation of those cells back into the person. However, in response the Examiner withdraws the statement. Applicants have argued that none of the references suggest the in vitro proliferation of neural stem cells, culture of the stem cells and transplantation back into the patient. However, Gage clearly suggests transplantation of autologous stem cells for therapeutic purposes and Hunter, Masters and Boyles discloses that oligodendrocyte precursors will produce apoD and apoE, a lipid involved in remyelination of demyelinated axons.

Applicants have argued that, with respect to claim 4, the passage cited by the Examiner describes a method of culturing cells in the presence of high heparin concentration that forces normally adherent cells to form floating aggregates and that the term "neurospheres" is not used in the reference. Applicants have further argued that the neurosphere defined in applicants' specification contain clonally derived nestin(+) cells that are nonadherent while the neurospheres used by Hunter are derived from various cells which have migrated together and they are not derived from the proliferation of a single cell. Applicants have further argued that the

Hunter fails to teach a culture method that utilizes neurospheres to produce clonally derived progeny. However, contrary to such arguments, neither claim 1 nor claim 4 requires the production of clonally derived neurospheres. Note that neither claim 1 nor 4 has the phrase "clonally derived neurospheres" and therefore Applicants' arguments are not persuasive. In addition, a careful reading of the specification shows that (page 8, definition of "neurosphere") that neurospheres, contrary to Applicants' arguments above, contain **some** cells which are nestin (+), are a cluster of cells derived from neural stem cells and is comprised of cells which are stem cells and/or progenitor cells and may or may not include differentiated cells. Contrary to Applicants' arguments, the combination of references renders obvious the claimed invention.

The rejection of claim 2 under 35 U.S.C. 103 as being unpatentable over Boyles taken with Hunter, Masters, Gage as applied to claims 1, 3-6 and 35 above and further in view of Morrison is maintained. Applicants have argued that none of the references teach the proliferation of neural stem cells in culture and that, at best, they teach the proliferation of progenitor cells in culture. However, claim 1 requires the culture of the neural stem cells to produce precursor cells and Morrison teaches the use of EGF to stimulate the proliferation and differentiation of glial cells.

Applicants have argued that the method of claim 2 calls for the proliferation of neural stem cells. However, contrary to such arguments, claim 2 merely requires the use of EGF.

The rejection of claims 7, 8, 10-13 and 15-17 under 35 U.S.C. 103 as being unpatentable over Boyles taken with Hunter, Masters and Gage is maintained. Applicants have argued that Hunter does not teach "isolation of neural stem cells" as the Examiner has alleged. However, Hunter discloses on page 236, column 2, last paragraph, preparation of primary cultures of neural cells derived from rat brains and those culture would contain neural stem cells since Hunter did not remove the stem cells. Note that the claim

does not claim an isolated, purified population of neural stem cells but only that the neural stem cells were isolated from the tissue of a donor. Therefore since Hunter discloses preparation of a primary neural cell culture wherein the cells were derived from the brain, Hunter discloses isolating neural stem cells from the tissue of a donor, lacking evidence to the contrary.

Applicants' arguments regarding the teachings of claims 1, 3-6 and 35 under 35 U.S.C. 103 with respect to the four references used by the Examiner have been addressed, above.

Applicants have argued that Gage was not able to show that implanted cells could migrate very far from the injection site to form cellular connections with host cells. However, the argument is irrelevant to the rejection as hand since no claim claims cells which must migrate. Note particularly that the claim claims causing the cells to come into contact with a demyelinated axon and therefore implies implantation at a desired site.

Regarding claims 15-17, Applicants have argued that Gage does not teach or suggest the transplantation of oligodendrocytes that are capable of remyelinating a recipient's axon. However, claims 15-17 do not require transplantation of oligodendrocytes and Boyles adequately discloses that oligodendrocytes and astrocytes produce apo D and E which are required for remyelination.

The rejection of claim 9 under 35 U.S.C. 103 as being unpatentable over Boyles taken with Hunter, Masters and Gage as applied to claims 7, 8 and 10-13 and 15-17 above and further in view of Morrison is maintained. Applicants have argued that Morrison does not teach the "proliferation and differentiation of glial cells". However, the Examiner has quoted Morrison directly (page 72, column 2, first full paragraph) and Applicants' interpretation of Morrison for purposes of argument are not persuasive. Hunter was not cited to teach stimulation of proliferation using EGF.

The following rejections are new grounds of rejection necessitated by Applicants' amendments to the claims.

Claim 14 is rejected under 35 U.S.C. 103 as being unpatentable over Boyles, Hunter, Gage and Masters as applied to claims 7, 8, 10-13 and 15-17 above, and further in view of Freshney. Freshney discloses methods for cloning various cell types. See pages 137-153. Freshney discloses on page 140, column 2, under "Multiwell dishes" that cloning by dilution makes harvesting easier and that the culture container must be checked to confirm that there is only one cell present or that only one cell gives rise to a colony. Therefore Freshney teaches the methods by which clonally derived neurospheres may be obtained.

It would have been obvious to one of ordinary skill to modify the method of cell culture of Boyles, Hunter, Gage and Masters by cloning the cells to obtain neurospheres derived from a single cell in view of the teachings of Freshney that cloning is useful to obtain pure cell strains (page 137, second full paragraph).

Accordingly, the modification of the method of cell culture of Boyles, Hunter, Gage or Masters by cloning the cells as suggested by Freshney in order to obtain a method to produce precursor cells from clonally derived neurospheres was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 31-34 are rejected under 35 U.S.C. 103 as being unpatentable over Hunter (of record) or Almazan et al. taken with Freshney. Hunter discloses producing glial cells comprising isolating neural stem cells from a

donor (Abstract). Hunter discloses proliferating the isolated neural stem cells in a culture medium containing B104 CM, conditioned medium containing growth factors, to produce precursor cells (Abstract, lines 2-3). Hunter discloses differentiating the precursor cells in a second culture medium which is substantially free of said growth factor to obtain glial cells, page 239, column 1, top paragraph. Note that a culture medium containing 33% B104 CM is considered to be substantially free of the growth factor. Hunter discloses use of aggregates, also known as neurospheres (See materials and methods). Almazan discloses that neurons and glial cells with the aggregates proliferate and differentiate in culture. Hunter and Almazan differ from the claims in that the references fail to disclosed clonally derived neurospheres. However, the secondary reference, Freshney, cures the deficiency. Freshney discloses methods for cloning various cell types. See pages 137-153. Freshney discloses on page 140, column 2, under "Multiwell dishes" that cloning by dilution makes harvesting easier and that the culture container must be checked to confirm that there is only one cell present or that only one cell gives rise to a colony. Therefore Freshney teaches the methods by which clonally derived neurospheres may be obtained.

Regarding claims 31-34, Hunter discloses that glial progenitors give rise to oligodendrocytes and astrocytes; therefore astrocytes and oligodendrocytes are glial cells. It would have been obvious to one of ordinary skill to modify the cell culture of Hunter or Almazan by cloning the cells to obtain neurospheres derived from a single cell in view of the teachings of Freshney that cloning is useful to obtain pure cell strains (page 137, second full paragraph).

Regarding claims 30-34, Hunter discloses use of aggregates, also known as neurospheres (See materials and methods).

Accordingly, the modification of the cell population of Hunter or Almazan by cloning the cells as suggested by Freshney in order to produce clonally derived neurospheres comprised of glial cells such as

oligodendrocytes and astrocytes was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

No claim is allowed.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703)308-4227.

An inquiry concerning this communication or earlier communications from the Examiner should be directed to Examiner Suzanne Ziska, Ph.D., at telephone number 703-308-1217. The Examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ms. Elizabeth Weimar, can be reached on (703) 308-0254.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SUZANNE E. ZISKA
PRIMARY EXAMINER
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9/2/94